Treatment of Hypertriglyceridemia-Induced Acute Pancreatitis With Insulin, Heparin, and Gemfibrozil: A Case Series

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Abstract

Hypertriglyceridemia is the third most common worldwide cause of acute pancreatitis. Resolving the underlying etiology is imperative for optimal management. This is especially true with regard to hypertriglyceridemia, as this etiology may cause more severe acute pancreatitis and worse symptoms than other causes of the disease. Many pharmacological treatment options for hypertriglyceridemia-induced acute pancreatitis (HTGP) have been proposed; however, the safety and efficacy for specific treatment regimens remain nebulous. At our institution, 6 patients, whose average Ranson criteria score were 5 and presenting triglyceride concentrations were 3501 mg/dL, were managed with a continuous infusion of insulin, subcutaneous heparin, and oral gemfibrozil for HTGP. Maximum insulin infusion rates ranged from 0.8 to 20.9 U/h. Half of the patients received nongemfibrozil cholesterol medication. Five patients experienced a resolution of HTGP (median day 3). The only adverse drug event was hypoglycemia in a single patient. Combination therapy with heparin, insulin, and gemfibrozil is safe and efficacious in quickly lowering serum triglyceride concentrations in HTGP. This combination warrants further study.

Keywords

gemfibrozil, heparin, hypertriglyceridemia, insulin, pancreatitis

Introduction

Hypertriglyceridemia is the third most common worldwide cause of acute pancreatitis.^{1,2} While providing supportive care and treatment for acute pancreatitis is crucial, treating the underlying etiology is also imperative.³ This is especially true with regard to hypertriglyceridemia, as this etiology may cause more severe acute pancreatitis and worse symptoms than other causes of the disease.^{1,4,5}

Mechanisms for hypertriglyceridemia-induced acute pancreatitis (HTGP) development have been postulated. Triglycerides in the pancreas are broken down by pancreatic lipases into their base components, glycerol and free fatty acids.⁶ The fatty acids accumulate in the pancreatic capillaries leading to blockage and ischemia, which can induce acute pancreatitis. This blockage can also increase the acidity of the pancreas, which predisposes the pancreas to acute inflammation through activation of trypsinogen.⁶ High blood viscosity caused by extremely elevated serum triglyceride levels could also be an initial reason for capillary blockage and acidosis.⁷

Plasmapheresis has been recommended as a nonpharmacological strategy to rapidly decrease serum triglycerides to resolve HTGP. The most effective way to employ plasmapheresis in HTGP may be as early as possible; however, no differences in mortality or complications have been found

between plasmapheresis and medication combinations.⁸ Although plasmapheresis is more expensive than pharmacological treatment, a formal cost-benefit evaluation has not been performed yet. Medication selection when treating acute pancreatitis should be based on the ability to correct the underlying etiology. Insulin increases the production of lipoprotein lipase (LPL), a tissue bound protein that catabolizes triglycerides into glycerol and free fatty acids and aids free fatty acid uptake into adipose tissue.⁶ Heparin binds to LPL, releasing it into the blood where it can break down circulating triglycerides.⁶ By enhancing the production and release of LPL, insulin and heparin are useful in reducing serum triglyceride concentrations. However, the effects heparin has on triglycerides are transient, as the drug also increases transport of LPL to the liver for degradation. For this reason, heparin monotherapy is likely not advantageous as a chronic, preventative therapy.⁴ Gemfibrozil is also proposed to lower

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triglycerides by increasing LPL activity. Increased fatty acid oxidation by stimulating peroxisome proliferator-activated receptor alpha and enhanced clearance of very Low-density lipoprotein (LDL) through the reduced action of apolipoprotein C-III are other proposed mechanisms of triglyceride lowering by gemfibrozil.⁸ Using a combination approach with insulin, heparin, and gemfibrozil should quickly reduce circulating triglycerides in patients with HTGP. Reducing triglyceride concentrations should result in a reduction in the duration and severity of the disease.⁴

Many pharmacological treatment options for HTGP have been put forth, which include insulin, heparin, and/or fenofibrates as part of the pharmacological treatment; however, the safety and efficacy for individual treatment options is still lacking.⁹ A proposed algorithm for treatment was put forth by Tsuang and colleagues that includes the use of insulin and oral antitriglyceride agents as a part of HTGP treatment and as a suggested means of reducing serum triglyceride concentrations.⁴ However, currently, no definitive guidelines exist for the treatment of HTGP.⁷ Previous studies on the treatment of HTGP with insulin, heparin, and/or fenofibrates include only case reports and small case series.^{3,5,6,9} These reports show that insulin alone, insulin in combination with heparin, and insulin in combination with gemfibrozil and niacin are all possibly effective management options for HTGP. This case series was performed to describe the effects of insulin, heparin, and gemfibrozil in combination for patients with HTGP.

Methods

Study Design and Setting

The institutional review board at our university approved this case series. Data were collected from electronic health records of patients admitted to a single tertiary care hospital between January 2008 and May 2015. This institution has 332 adult beds, 52 of which are located in an intensive care unit (ICU). There was no formal protocol for HTGP management in place at the institution during the study period.

Patients

Patients were eligible for inclusion if they were at least 18 years of age, were diagnosed with HTGP, and received the combination of a continuous infusion of insulin, subcutaneous heparin, and oral gemfibrozil concomitantly for the intention of treating HTGP. These medications are not approved by the US Food and Drug Administration for this indication. Patients who were receiving a continuous infusion of insulin and developed blood glucose values below 200 mg/dL were provided dextrose infusions to continue infusion therapy. Patients excluded from this study were those who had a diagnosis of acute pancreatitis not secondary to hypertriglyceridemia. Also excluded were patients diagnosed with hypertriglyceridemia-induced acute pancreatitis (HTPG) who were

transferred from an outside hospital after treatment began without sufficient records available to track the progress of that treatment.

Data Collection and Study Outcomes

The primary effectiveness outcome was time to resolution of HTGP, defined as achievement of a serum triglyceride concentration below 1000 mg/dL. Both 500 and 1000 mg/dL have been used as target serum triglyceride concentrations without noticeable differences in complications^{1,4,9}; at our institution, we use 1000 mg/dL. The primary safety outcome was development of complications associated with the therapies employed in the management of HTGP. Baseline and clinical characteristics were determined, including Charlson comorbidity index score, Ranson criteria score, and laboratory values relevant to the management of HTGP.

Statistical Analysis

The primary outcomes and clinical characteristics were evaluated with counts and percentages. The primary effectiveness outcome could only be evaluated in patients for whom a serum triglyceride concentration below 1000 mg/dL was reported. All data were analyzed using Excel 2013 (Microsoft Corporation, Redmond, Washington).

Results

Of the patient charts reviewed, 6 met the criteria for inclusion. The average Ranson criteria score in our cohort was 5 (range: 2-8), and 5 of the 6 patients had a Ranson criteria score of 3 or greater, indicating severe pancreatitis. The average triglyceride level upon admission was 3501 mg/dL (range: 1594 to greater than 5000), average amylase was 526 U/L (142 to 1282), and average lipase was 939 U/L (115 to 2730). Other baseline and clinical characteristics are provided in Table 1. All patients received a continuous infusion of insulin (initiated at 1-2 U/h), subcutaneous heparin, and oral gemfibrozil for at least 1 day at the start of the treatment course. Half of the patients also received a statin and 1 patient received niacin in addition to gemfibrozil (Table 2).

Five patients experienced a resolution of HTGP. Patients achieved this target on different days: day 3 ($n = 3$), day 4 ($n = 1$), and day 5 ($n = 1$). One patient's triglyceride levels were not monitored beyond day 2, and attainment of treatment success could not be ascertained definitively. One patient developed an episode of hypoglycemia. No other adverse drug events were seen (Table 2).

Discussion

Combination therapy with heparin, insulin, and gemfibrozil is safe and efficacious in lowering the serum triglyceride concentration in patients experiencing HTGP. Half of the

Table 1. Baseline Characteristics.

Patients	1	2	3	4	5	6
Age (y)	46	45	56	38	44	30
Charlson comorbidity index	1	1	2	1	0	1
Ranson criteria index	6	7	3	8	2	5
Admission values						
Triglyceride (mg/dL)	>5000	>5000	>5000	3949	4960	1594
Glucose (mg/dL)	393	316	855	373	129	389
Lipase (U/dL)	800	1064	313	115	611	2730

Table 2. Clinical Course.

Patients	1	2	3	4	5	6
Time until triglyceride <1000 mg/dL (d)	4	3	—	3	3	5
Duration of insulin infusion (d)	4	2	1	3	2	4
Maximum insulin infusion rate (U/h)	4	10	5	21	0.8	20.9
Nongemfibrozil cholesterol medication	Statin, niacin	—	—	—	Statin	Statin
Intravenous fluid volume in first 48 h (mL)	6200	7700	4200	6040	7600	6445
Plasmapheresis	No	Yes	No	No	No	No

patients in this study reached a triglyceride level below 1000 mg/dL within 3 days, while the only adverse event was one instance of hypoglycemia.

Hypertriglyceridemia is the underlying etiology in 1% to 10% of acute pancreatitis cases.^{1,10-12} With rare exception, triglyceride levels must exceed 1000 mg/dL to induce acute pancreatitis.^{4,10,13,14}

In our cohort, the average serum triglyceride, amylase, and lipase concentrations were similar to those of another comparable case series performed by Coskun and colleagues that investigated treatment with insulin alone. The most notable difference was that study featured a much higher and wider triglyceride concentration range.¹² Five of the 6 patients in this cohort had severe pancreatitis per Ranson criteria compared with 6 of 12 patients in the Coskun case series. The lab values and clinical presentation of the patients in our cohort are representative of typical patients with HTGP who are managed in the ICU setting.

The initial treatment of acute HTGP should be similar to that of other types of acute pancreatitis, as there is no definitive evidence that outcomes of HTGP differ from those of pancreatitis caused by other etiologies.^{10,12} The role of LPL in the reduction of triglycerides in the body suggests that it is a promising target in the treatment of HTGP. The mechanisms of insulin and heparin in producing and enhancing the effects of LPL are encouraging in the management of HTGP. In our cohort, patients received insulin and heparin, as well as gemfibrozil, an agent used specifically for the reduction of serum triglycerides with 3 possible mechanisms of action for this effect. Due to the nature of combination therapy, it was impossible to discern which agent was attributable for specific effects; however, it was determined that the combination therapy as a whole was effective. In the Coskun study,

patients were given regular insulin intravenous infusions in 5% dextrose to achieve serum glucose concentrations not exceeding 200 mg/dL. Although there was no specific mention of the patients being treated with heparin as part of their treatment protocol, most patients did receive heparin as a standard of care at this hospital for acutely and critically ill patients.¹² In contrast to the patients in our cohort, a specific triglyceride-lowering agent was not added to the treatment regimen in the Coskun study. In our cohort, 1 patient did receive plasmapheresis in addition to the evaluated combination therapy, which also has been shown to be an effective treatment strategy in HTGP.^{14,15} Given the timely resolution of HTGP with pharmacological therapy, addition of plasmapheresis should be investigated to determine whether additional benefits are provided and how safety is affected.

In our cohort, the time to resolution ranged from 3 to 5 days, with half of the patients achieving resolution on day 3. In the Coskun study, patients also met their triglyceride target goal by day 3, although the goal in that study was less than 500 mg/dL rather than the less than 1000 mg/dL goal in this one.¹² The similarity in time frame to reaching different goals may be due to the difference in beginning triglyceride levels between the 2 groups. Another possibility may be attributable to the patients in our cohort taking gemfibrozil in the outpatient setting as well.

In another study, Thuzar and colleagues observed 10 patients with extreme hypertriglyceridemia (serum triglyceride concentrations exceeding 4428 mg/dL), 5 of whom had acute pancreatitis.⁹ The triglyceride concentrations of these patients on admission more closely resemble to the majority of the patients in our cohort than those of the Coskun study.^{9,12} The Thuzar study used insulin with and without fasting administration as treatment for HTGP and showed resolution

of hypertriglyceridemia on day 3 and 6, respectively, which was similar to this study.⁹

The combination of insulin, heparin, and gemfibrozil is a safe treatment option for HTGP. In our cohort, there was one instance on hypoglycemia, which is a known adverse event of insulin use. It is important to monitor patients receiving insulin therapy very closely to prevent or react to this adverse effect. Therefore, patients receiving a continuous infusion of insulin for HTGP should be admitted to the ICU, where a closer level of nursing care can be provided. Adverse events of therapy were only reported in one other study using these agents in treating HTGP.⁹ In the Thuzar study, one case of a pancreatic pseudocyst was reported, though this is likely a complication of the disease state and not the treatment provided.^{5,6,9,12}

Combination therapy with heparin, insulin, and gemfibrozil is safe and efficacious in quickly lowering serum triglyceride concentrations in HTGP. This combination warrants further study against a strategy that also includes plasmapheresis or employs plasmapheresis as monotherapy.

Authors' Note

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Declaration of Conflicting Interests

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